PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 49/04	A2	(11) International Publication Number: WO 00/21577
		(43) International Publication Date: 20 April 2000 (20.04.00)

(21) International Application Number: PCT/GB99/03344

(22) International Filing Date: 8 October 1999 (08.10.99)

(30) Priority Data:
9822158.3 9 October 1998 (09.10.98) GB

(71) Applicant *(for all designated States except US)*: NYCOMED IMAGING AS [NO/NO]; Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo (NO).

(71) Applicant *(for GB only)*: COCKBAIN, Julian [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: McINTIRE, Gregory, Lynn [US/US]; Nycomed Inc., 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087 (US). BACON, Edward, Richard [US/US]; Nycomed Inc., 466 Devon Park Drive, P.O. Box 6630, Wayne, PA 19087 (US).

(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOSITIONS

(57) Abstract

Water-soluble iodinated X-ray contrast agents can stabilise certain particulate compositions comprising vesicles or liquid droplets for thermal sterilisation. Such contrast agents also enhance the physical stability of particulate compositions to settling during storage.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macédonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Compositions

This invention relates to a new class of stabiliser for particulate compositions and in particular to new formulations which facilitate the heat sterilisation of such compositions.

Particulate suspensions and dispersions such as emulsions and vesicles suspensions (e.g. containing micelles, microbubbles, microballoons or liposomes) have a wide variety of medicinal and non-medicinal uses.

The particles (ie. droplets and vesicles) in such compositions are generally from approximately 1 nm to 1 mm in diameter, and often have a surface modifier adsorbed onto their surface. As droplets and vesicles are not rigid solids and can coalesce, the vesicles or droplets in such compositions are susceptible to volume changes and often do not survive the elevated temperatures and pressures required for thermal sterilisation without either particle destruction or significant particle size distribution changes.

In the development of particulate dispersions or suspensions for parenteral use, product sterilisation represents a major challenge owing to the sizes of the particles. The two most common sterilisation techniques are sterile filtration and thermal sterilisation, e.g. autoclaving or steam sterilisation. Sterile filtration is sufficient to remove most viruses and bacteria but most particles, due to their size, generally cannot be sterile filtered. Thermal sterilisation is also problematical as it often leads to significant increases in particle size as a result of heat induced aggregation and/or particle growth, rendering the resulting particles unusable.

Particulate compositions for parenteral administration generally require the use of a surfactant as a surface modifier, for example a surfactant e.g. to prolong blood residence time, to stabilize the suspension or dispersion, to target the particles to particular biological sites, to prevent particle aggregation, etc. Thus for example in US Patent No. 5,352,459 (Hollister et al.) a purified polymeric surfactant is employed as the surface modifier for adsorbing onto the surface of nanoparticles (ie. nanometer sized particles), while in US Patent No. 5,569,448 (Wong et al) a block copolymer linked to at least one anionic group is suggested as a surface modifier for adsorbing onto the surface of nanoparticles.

Since the presence of ionic surfactants can cause particle agglomeration, and may cause toxicity problems and since particle agglomeration is undesirable for parenterally administered particulate compositions, it is clearly desirable to use non-ionic surfactants. The use of non-ionic surfactants is further desirable since they impart steric stability. Unfortunately, where a non-ionic surfactant is used as a surface modifier for such particulate compositions, the problems of thermal sterilisation are exacerbated as at elevated temperatures such non-ionic surfactants undergo a well-known phase separation referred to as a cloud point, which may cause the compositions to flocculate or coalesce.

The aggregation of the particles upon heating is directly related to the precipitation and/or phase separation of the surface modifier at temperatures above the cloud point of the surfactant where the bound surfactant molecules are likely to dissociate from the particles and precipitate and/or phase separate, leaving

the particles unprotected. The unprotected particles can then aggregate into clusters of particles. Upon cooling, the surfactant redissolves into the solution which then coats the aggregated particles and prevents them from dissociating into smaller ones.

In order to prevent this aggregation, cloud point modifiers are currently the preferred means for stabilising nanoparticle suspensions, emulsions and liposomes during heat sterilisation. The cloud point modifier is added in an amount sufficient to increase the cloud point of the surface modifier to a temperature greater than that required for heat sterilisation.

In US Patent No. 5,346,702 (Na et al.) a composition is disclosed comprising nanoparticles having a surface modifier adsorbed on the surface thereof and a non-ionic cloud point modifier (preferably a poloxamine such as Tetronic 908).

In US Patent No. 5,336,507 a nanoparticle composition is disclosed in which a charged phospholipid is utilised as the cloud point modifier. This modifier is preferably dimyristoyl phosphatidyl glycerol (DMPG).

In US Patent No. 5,298,262 (Na et al) an anionic or cationic surfactant is suggested as a cloud point modifier. A preferred anionic cloud point modifier is stated to be dioctylsulfosuccinate.

However, cloud point modifiers do not work for every particle suspension. Also, ionic cloud point modifiers such as dimyristoyl phosphatidyl glycerol, are not preferred due to both safety and efficacy concerns. For example, the cloud point modifier dioctylsulfosuccinate is hemolytic to red blood cells.

Moreover, one of the most preferred classes of cloud point modifiers, the polyethyleneglycols, whilst functioning well, must be used at elevated concentrations where their relative safety in large volume parenteral administrations remains untested. Furthermore, polyoxyethyleneglycol (PEG) polymers suffer from chemical instability in the presence of oxygen and light. Additionally, trace amounts of common metal impurities can act as catalysts for the degradation reactions of the polyethyleneglycol molecules. These problems are also encountered in the lyophilised state and thus PEG formulations require to be degassed with an inert gas and stored in metal free containers in the dark.

We have now surprisingly found, however, that certain particulate compositions can be stabilised for thermal sterilisation by water-soluble, iodinated X-ray contrast agents. These water-soluble, iodinated X-ray contrast agents afford particle size stability during heat sterilisation of particulate compositions and provide both process and safety advantages over conventional cloud point modifiers. Although it is not known what the operative mechanism of protection is for these agents, it is known that they are not cloud point modifiers for the commonly used non-ionic surfactants such as Pluronic F-108.

Thus viewed from one aspect the invention provides a diagnostic or therapeutic particulate composition said composition comprising a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets (e.g. the discontinuous phase of an emulsion), and, preferably, a physiologically tolerable liquid dispersion medium (generally an aqueous medium).

Viewed from a further aspect the invention provides a process for the preparation of a sterile therapeutic or diagnostic particulate composition, said process comprising thermally sterilising (e.g. by steam heat sterilizing, for example by autoclaving) a composition comprising a physiologically tolerable liquid dispersion medium (generally an aqueous medium), a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

Viewed from a yet further aspect the invention provides the use of a physiologically tolerable water-soluble iodinated X-ray contrast agent for the manufacture of a therapeutic or diagnostic composition for use in a method of therapy or diagnosis (e.g. in a method involving a diagnostic imaging procedure), said composition comprising a physiologically tolerable liquid dispersion medium (generally an aqueous medium), a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

Viewed from a yet further aspect the invention provides a method of therapy or diagnosis of a human or non-human animal (preferably a vascularised animal, e.g. a mammalian, reptilian or avian animal) body, said method comprising administering to said body a therapeutically or diagnostically effective amount of a sterile composition comprising a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

Viewed from a yet still further aspect the invention

provides a method of generating an image of a human or non-human animal (preferably a vascularised animal, e.g. a mammalian, reptilian or avian animal) body, said method comprising, after administering to said body a diagnostically effective amount of a sterile composition comprising a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets, generating an image of at least part of said body (e.g. using an imaging modality such as MR imaging X-ray imaging (e.g. CT imaging), ultrasound imaging, magnetotomography, electrical impedance tomography, SPECT, PET and scintigraphy).

In the present invention, the water-soluble iodinated X-ray contrast agent is used in a quantity sufficient to achieve a stabilising effect, e.g. a concentration sufficient to stabilise said composition for thermal sterilisation or a concentration sufficient to reduce the tendency of the composition to settling during storage.

The water-soluble iodinated X-ray contrast agents used according to the invention will generally contain iodophenyl moieties, e.g. diiodophenyl or more preferably triiodophenyl moieties, and may contain one or more, e.g. 1, 2 or 3 such iodophenyl moieties per molecule. The iodophenyl rings will in such an event generally be substituted by solubilizing groups, e.g. ionic groups or more preferably non-ionic groups, for example groups containing mono or polyhydroxy-C_{1-10}-alkyl moieties optionally linked to the phenyl ring via an amide or ether function. A wide variety of such iodophenyl agents are known from the literature and many are available commercially (see Martindale "The Extra Pharmacopoiea", 30th Edition, 1993, The Pharmaceutical Press, London, pages 707 to 711). Examples include

iohexol, ioversol, iopamidol, iopentol, iodixanol, iopromide, iomeprol, ioxilan, iosimide, metrizamide, iotasol and iotrolan.

The use of water-soluble, iodinated X-ray contrast agents as stabilizers for the heat sterilization of particle suspensions will provide advantages such as not requiring the formulation to be oxygen-free, minimizing the requirement for metal ion free dispersion media and metal-free containers, and excellent safety at the high concentrations currently used in large volume parenteral administrations. These agents are also readily available and, advantageously, have low viscosities at the concentrations required for thermal sterilization of particulate compositions.

The water-soluble, iodinated X-ray contrast agents used according to the present invention have a well documented chemical stability and their formulations can be lyophilized and may possibly provide completely GRAS (generally regarded as safe) formulations for the novel particulate compositions of interest.

Moreover, in some cases where cloud point modifiers such as PEG 1450 were ineffective in the stabilization of particle size after thermal sterilization, the water-soluble, iodinated X-ray contrast agents of the invention were successful at maintaining particle size. Thus, in addition to the process and storage stability advantages, the use of these novel agents to achieve particle size stability during heat sterilization will open this technology to additional particulate agents which would otherwise have failed to meet sterilization requirements.

The water-soluble, iodinated X-ray contrast agents used according to the invention also increase the density of

the solution phase thus enhancing the physical stability of the compositions to settling during storage.

The addition of increasing amounts of, for example, iohexol to aqueous emulsions or vesicular compositions will reduce the tendency of the particles towards settling (sedimentation) over time in the container. Settling is a density driven process, i.e. the continuous phase is near the density of water while the particles may be significantly more dense, e.g. with density values > 2.0 g/mL in the case of liquid droplets of water insoluble iodinated X-ray contrast agents. Thus, addition of, for example, iohexol to the continuous phase can be used to increase the density of the continuous phase such that the density difference between the particles and the continuous phase will decrease.

This increase in continuous phase density by the use of water soluble iodinated X-ray contrast agents can be used in the stabilization of any suspension which would benefit from increased continuous phase density, for example, agricultural formulations where particle settling and aggregation both on the shelf and during administration is a concern.

Thus viewed from a further aspect the invention provides a particulate composition, preferably a sterile composition, comprising an aqueous solution of an iodinated X-ray contrast agent which solution contains and is substantially isodense with a water-insoluble particulate material, e.g. a catalyst, a pharmaceutical or veterinary agent, a dietary supplement, etc.

By substantially isodense it is meant that the concentrations of the X-ray contrast agent in the aqueous medium (which may of course contain other

dissolved substances, for example co-catalysts, pharmaceutical or veterinary agents, dietary supplements, stabilizers, antioxidants, flavors, aromas, colours, osmolality adjusting agents, pH adjusting agents or buffers, etc) is such that the density difference between the solution and the particulate material is sufficiently low that no significant particle sedimentation occurs over a prolonged storage period, e.g. at least one week, preferably at least one month, more preferably at least three months.

The compositions which may be stabilized according to the invention are those comprising particles such as liposomes, polymeric particles, inorganic particles such as catalysts, viral particles e.g. those used for antisense or sense DNA delivery, bacterial particles e.g. those used for DNA delivery, or compositions in the form of emulsions, prion particles and other peptide and protein particles or aggregates.

The X-ray contrast agents may likewise be used to stabilize water-in-oil emulsions by making the aqueous droplets substantially isodense with the continuous oil phase. Such compositions form a further aspect of the invention. Viewed from this aspect the invention provides a water-in-oil emulsion wherein the discontinuous water phase contains a dissolved iodinated X-ray contrast agent and is substantially isodense with the continuous oil phase.

The water-soluble iodinated X-ray contrast agents may also be used to stabilize particle suspensions which might experience either temporary heat extremes or continued elevated temperature such as suspensions exposed to diurnal cycles of sunlight and darkness. Also envisaged is their use for physical and chemical stabilization for liquid crystal displays in flat panel

displays, CRT displays, watch displays, etc. The same properties which make these agents useful for particle stabilization may well extend the utility of these devices past their current useful lifetimes.

Water-soluble iodinated X-ray contrast agents particularly useful according to the invention are preferably molecular weight less than 2000 Daltons and include iohexol (Omnipaque®), iopamidol (Isovue™), iopentol (Imagopaque®), ioxilan and iodixanol (Visipaque®). The compositions according to the invention may contain a single water-soluble iodinated X-ray contrast agent or a mixture of two or more water-soluble, iodinated X-ray contrast agents.

For thermal sterilisation, the quantity of water-soluble iodinated X-ray contrast agent used will depend upon the nature and quantity of the other excipients present in the composition but will be a quantity sufficient to stabilise the composition for thermal sterilisation. The necessary amount may readily be determined by the person of ordinary skill in pharmaceutical science. Generally, the amount will be in the range 5-40% by weight (relative to the weight of the aqueous phase of the composition), preferably in excess of 15%, most preferably in excess of 20% by weight.

For improving physical stability to settling, the quantity of water-soluble, iodinated X-ray contrast agent used will depend upon the nature and quantity of the other excipients present in the composition but will be a quantity sufficient to increase the physical stability to settling of the composition. The necessary amount may readily be determined by the person of ordinary skill in pharmaceutical science. Generally, the amount will be in the range 5-40% by weight (relative to the weight of the aqueous phase of the

composition), preferably in excess of 15%, most preferably in excess of 20% by weight.

The water-soluble, iodinated X-ray contrast agents useful according to the invention are commercially available or can be prepared according to methods well-known in the art, for example the methods disclosed in SE-7706792-4, by Gulbrandsen in Kjemi No. 6/90, pages 6-8, NO-160918, WO 9808805 and WO 9808804.

The surfactants used in the compositions of the invention are preferably non-ionic and may be for example alkaline oxide polymers or copolymers, e.g. poloxamers such as the pluronics (e.g. Pluronic F68 and 108 which are block copolymers of ethylene oxide and propylene oxide) or poloxamines such as the tetronics (e.g. Tetronic 908) and the carbowaxes (which are polyethyleneglycols (PEGs)), tyloxapol, polyvinylpyrrolidone, P-79, and PEG-modified phospholipids. These will generally be used in relatively minor quantities e.g. 0.1-10% by weight and are normally used at quantities sufficient to ensure that a stable composition can be formed.

The number of particles within the particulate compositions of the invention will depend on the nature and quantity of the other excipients present, the use of the composition, e.g. whether for therapeutic or diagnostic use, the nature of the active agent, the particular animal species and the size of the animal to be treated but the necessary amount may readily be determined by the person skilled in pharmaceutical science. Generally, the amount of particles in the compositions of the invention will be in the range 0.1 to 45% by weight, preferably 1 to 30% by weight.

Heat sterilisation in the process of the invention may

be carried out in conventional fashion, e.g. by autoclaving (steam or moist heat sterilisation). Sterilisation is preferably effected for at least 15 minutes, preferably 20 minutes or more at a temperature of 121°C or slightly higher. In some cases, sterilisation is performed at lower temperatures for longer times e.g. 110°C for 90 minutes. The compositions of the invention are useful in such conditions.

The compositions of the invention can be lyophilised and the water-soluble, iodinated X-ray contrast agents described herein are suitable for the stabilisation of such compositions.

The compositions of the invention preferably have an aqueous carrier medium, or if in dried form are preferably suspended in such a medium prior to administration. For example in a physiologically tolerable saline medium or in water for injection.

Besides liquid droplet or vesicle-containing compositions, the water-soluble iodinated X-ray contrast agents may be used according to the invention to stabilize, e.g. against settling or thermal treatment, other particulate suspensions or dispersions which may or may not also contain a surfactant, e.g. a non-ionic surfactant. Examples of such particulates include inorganic particles, polymer particles, viral particles, bacterial particles, catalyst particles, etc.

The publications referred to herein are hereby incorporated by reference.

The invention will now be described further by the following non-limiting Examples.

Example 1 - Synthesis of 3,5-Dihexylmethoxybenzene

To a stirred solution of 3,5-dichloroanisole (210g, 1.19 mol) in t-butylmethyl ether (1.6L) at room temperature under nitrogen, was added nickel (II) diphenyl-phosphinoethane dichloride (DPPE; 1.6g, 0.25 mole %). A solution of hexylmagnesium bromide (2M in diethyl ether; 1 .5L, 2.5 eq.) was then added dropwise over a 1 hour period followed by stirring at room temperature for 12 hrs. After refluxing the solution for 8 hours, NMR analysis of the mixture revealed residual starting anisole, so the reaction was cooled and recharged with additional catalyst (0.5g) and reheated to reflux. After heating an additional 48 hours, NMR analysis indicated essentially complete conversion, so the the mixture was cooled and carefully added to 2L of cold aqueous 1N HCl. The organic layer was separated and the aqueous layer was washed with t-butylmethyl ether (1 x 500 ml). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through a plug of silica gel (500g) eluting with hexanes. The filtrate was evaporated to dryness under vacuum to give 336g of colorless oil. The crude product was then purified by wipe film distillation (110°C/0.01 torr) to give 206g (63%) of the title compound. The ^{1}H-NMR (300 MHz) spectrum was consistent with desired structure. Title compound: Calculated for $C_{19}H_{32}O$: C82.55; H 11.67; Found: C 82.20; H 11.52.

Example 2 - Synthesis of 3,5-Dihexyl-2,4,6-triiodomethoxybenzene

To a suspension of 3,5-dihexylmethoxybenzene (27.6g, 0.1 mol) and N-iodosuccinimide (78.4g, 0.35 mol; freshly recystallized from acetone) in 300 ml of 1,2-dichloroethane under nitrogen was added trifluoromethanesulfonic acid (15.0g, 9.0 ml, 0.1 mol)

dropwise over a 10 minute period. The resulting solution was heated on a steam bath for 1 hour; after cooling briefly, an additional quantity of N-iodosuccinimide (11.2g, 0.5 mol) was added and heating continued for 1 hour at which point TLC analysis of an aliquot indicated that iodination had proceeded to completion. The solution was cooled to room temperature, washed with water and the organic layer dried over anhydrous $MgSO_4$. The solution was then concentrated and the crude red-orange product was filtered through a pad of silica gel, eluting with hexanes. The combined organic layer (~2L) was washed with 10% aqueous $Na_2S_2O_3$ until colorless, dried over $MgSO_4$, filtered and concentrated under high vacuum to give the product as a viscous, colorless oil (53.4g, 82%) that crystallized on standing to give a white solid, mp 38-40°C. The ^{1}H-NMR (300 MHz) spectrum was consistent with desired structure.
Title compound: Calculated for $C_{19}H_{29}I_3O$: C34.89; H 4.47; I 58.21; Found: C 34.79; H 4.46; I 58.22.

Example 3 - Synthesis of 3,5-Dihexyl-2,4,6-triiodophenol

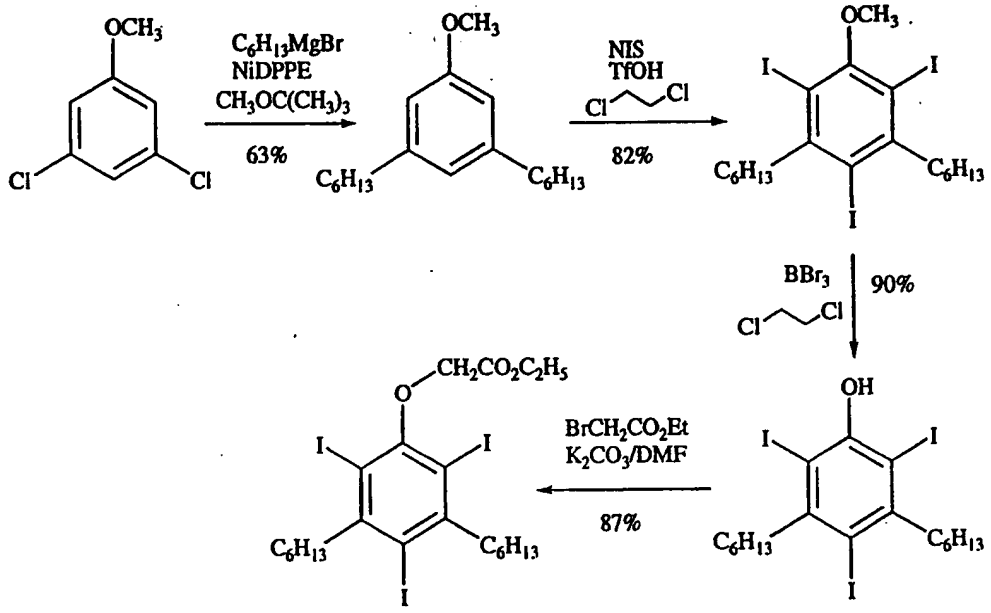
To a solution of 3,5-dihexyl-2,4,6-triiodomethoxybenzene (438.4g, 0.67 mol) in 1,2-dichloroethane (1500 ml) at room temperature under nitrogen, was added dropwise over a 30-45 minute period, boron tribromide (201 g, 0.8 mol, 1.2 eq.). After refluxing for 18 hours, the dark solution was cooled and slowly poured into ice-water. The mixture was extracted with dichloromethane (1L) and the combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under vacuum to give the crude product as a solid. Recrystallization from ethanol gave the pure product in two crops (384g, 90%) as a white solid, mp 76-77°C. The ^{1}H-NMR (300 MHz) spectrum was consistent with desired structure.

Title compound: Calculated for $C_{18}H_{27}I_3O$: C33.77; H 4.25; I 59.47; Found: C 33.88; H 4.14; I 59.39.

Example 4 - Synthesis of Ethyl 5-(3,5-Dihexyl-2,4,6-triiodophenoxy)acetate

To a magnetically stirred mixture of 3,5-dihexyl-2,4,6-triiodophenol (15.00g, 23.4 mmol) and potassium carbonate (6.48g, 46.8 mmol) in DMF (35 ml) at room temperature was added ethyl bromoacetate (4.70g, 3.1 ml, 28.1 mmol). The mixture was then stirred under nitrogen for 16 hours, and poured into 200 ml water. The aqueous mixture was extracted with 200 ml ethyl acetate. The ethyl acetate layer was washed with 75 ml of saturated NaCl solution, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under vacuum at 40°C to give a brown oil. The oil was purified by silica gel chromatography (4% ethyl acetate/hexane elution) to give 14.77g (87%) of analytically pure product as a white solid, mp 51-53°C, after drying under high vacuum at 80°C for 30 minutes. The ^{1}H-NMR (300 MHz) spectrum and mass spectral data (LSIMS: M$^+$ 726) were consistent with desired structure.
Title compound: Calculated for $C_{22}H_{33}I_3O_3$: C 36.39; H 4.58; I 52.42; Found: C 36.39; H 4.50; I 52.06.

The Synthesis of ethyl 5-(3,5-dihexyl-2,4,6-triiodophenoxy)acetate is illustrated in Scheme 1 below:



Example 5 - The use of water soluble iodinated contrast agents to stabilize oil-in-water emulsions to steam sterilization

An oil-in-water emulsion was prepared by mixing 3 gm of an oil soluble iodinated contrast agent ethyl 5-(3,5-dihexyl-2,4,6-triiodophenoxy)acetate (2 gm) of sesame seed oil, 240 mg of egg lecithin, and 300 mg of a polymeric surfactant stabilizer designated as P-79 (preparation of P-79 is disclosed in Example 2k of WO 96/02434) with water bath sonication for 10 minutes. Enough water was added to make a total volume of 20 ml. This mixture was heated to 70°C to melt the contrast agent before the entire suspension was processed through a Microfluidics microfluidizer at medium pressure for approximately 20 to 30 pump cycles until the resulting white emulsion particle size stabilized near 100 nm.

The resulting emulsion was characterised and then heat sterilized under conventional settings of 121°C for 20 minutes. The resulting sterile emulsion was again characterised with the results shown below.

Sample	Avg Particle Size (nm)	pH	Osmolality (mOsm/kg)	
no heat	108(40)		6.10	97
heat sterilized	113(50)		4.66	--

The same emulsion was prepared in the same manner with the addition of enough iohexol to make the final emulsion 30% by weight iohexol. The characteristics of this emulsion are given below before and after autoclave sterilization

Sample	Avg Particle Size (nm)	pH	Osmolality (mOsm/kg)	
no heat	117(43)		4.40	---
heat sterilized	121(43)		7.01	289

The addition of iohexol to this emulsion resulted in a much smaller change in pH during heat sterilization while particle size remained stable. The increase in osmolality from the original emulsion is generally thought to be a destabilizing influence for heat sterilization; however, in this case, the emulsion is stable to heat sterilization both physically and chemically with the addition of iohexol.

Example 6 - The use of water soluble iodinated contrast agents to stabilize liposomes during heat sterilization

Liposomes were prepared from a 10 to 1 mole ratio mixture of hydrogenated phosphatidyl choline (H-PC) to hydrogenated phosphatidyl serine (H-PS) by extruding through multiple stacked 1 micron filters under pressure (ie. 100 bars). The final concentrations of H-PC and H-PS were reached by dilution with a solution of 50 mg sucrose/ml so that the liposomes were 64.4 mg H-PC/ml and 6.4 mg H-PS/ml. In addition, the suspension was made 1% (wt/vol%) in the polymeric surfactant designated P-79. This nonionic surfactant was intended to provide "stealth" qualities to the liposomes for prolonged vascular residence and passive targeting. These "empty" liposomes were diluted in the following manner and characterised for average particle size followed by conventional heat sterilization and repeated particle size determination using the Horiba 910a light scattering instrument. The results are given below:

		Average Particle Size (nm)	
		Before	After
Diluent*	mg/ml	Autoclave	Autoclave
+1 ml water	0	381(114)##	85% @ 389 nm 15% @ 17 μm
+0.2 ml iohexol** (0.8 ml water)	75.5	362(104)	93% @ 296 nm 7% @ 15 μm
+0.5 ml iohexol (0.5 ml water)	188.8	360(98)	265 (56) nm
+1 ml iohexol	377.5	333(85)	233 (57) nm
+0.2 ml iodixanol'	65.2	368(109)	95% @ 339 nm

(0.8 ml water)			5% @ 17 μm
+0.5 ml iodixanol (0.5 ml water)	163.0	361(104)	231 (53) nm
+1 ml iodixanol	326.0	349(97)	215 (53) nm

* All samples begin with 1 ml of "empty" liposome formulation

** Iohexol 350 (ie. Omnipaque 350)

\# Iodixanol 320 (ie. Visipaque 320)

Standard Deviation

The results demonstrate that the addition of sufficient water soluble, iodinated contrast agent to the liposomes will enhance particle size stability to heat sterilization.

Claims

1. A diagnostic or therapeutic particulate composition said composition comprising a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

2. A composition as claimed in claim 1 further comprising a physiologically tolerable liquid dispersion medium.

3. A composition as claimed in claim 2 wherein said medium is aqueous.

4. A composition as claimed in any one of claims 1 to 3, wherein said contrast agent is selected from the group consisting of iohexol, ioversol, iopamidol, iopentol, iodixanol, iopromide, iomeprol, ioxilan, iosimide, metrizamide, iotasol and iotrolan.

5. A composition as claimed in claim 4 wherein said contrast agent is iohexol, iopamidol, iopentol, ioxilan or iodixanol.

6. A composition as claimed in any one of claims 1 to 5, wherein said surfactant is selected from the group consisting of poloxamers, poloxamines, tyloxapol, polyvinylpyrrolidone, P-79 and PEG-modified phospholipids.

7. A composition as claimed in any one of claims 1 to 6, wherein said composition comprises 0.1 to 10% by weight surfactant.

8. A composition as claimed in any one of claims 1 to 7, wherein said composition comprises 5 to 40% by weight

X-ray contrast agent.

9. A composition as claimed in any one of claims 1 to 8, wherein said particulate component is a liposome.

10. A composition as claimed in any one of claims 1 to 8, wherein said particulate component forms part of an emulsion.

11. A process for the preparation of a sterile therapeutic or diagnostic particulate composition, said process comprising thermally sterilising a composition as claimed in any one of claims 1 to 10.

12. The use of a physiologically tolerable water-soluble iodinated X-ray contrast agent for the manufacture of a therapeutic or diagnostic composition for use in a method of therapy or diagnosis, said composition comprising a physiologically tolerable liquid dispersion medium, a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

13. A method of therapy or diagnosis of a human or non-human animal body, said method comprising administering to said body a therapeutically or diagnostically effective amount of a sterile composition comprising a physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets.

14. A method of generating an image of a human or non-human animal body, said method comprising, after administering to said body a diagnostically effective amount of a sterile composition comprising a

physiologically tolerable surfactant, a physiologically tolerable water-soluble, iodinated X-ray contrast agent and a particulate component selected from vesicles and liquid droplets, generating an image of at least part of said body.

15. A particulate composition, preferably a sterile composition, comprising an aqueous solution of a water-soluble iodinated X-ray contrast agent which solution contains and is substantially isodense with a water-insoluble particulate material, a pharmaceutical or veterinary agent, a dietary supplement.

16. A method of enhancing the physical stability of particulate composition comprising vesicles or liquid droplets comprising adding to said composition a water-soluble, iodinated X-ray contrast agent.